

Medical Management of Epilepsy

Guideline: People with epilepsy will be identified, evaluated by a primary care prescriber, and if treatment is indicated, be placed on the most effective and least toxic medication at the optimal dose. Neurological consultation may be included in the medical plan of care.

DEFINITIONS:

Individual's record: A permanent legal document that provides comprehensive information about the individual's health care status.

Primary care prescribers: Physicians, nurse practitioners, and physician's assistants who provide primary care services and are authorized to prescribe medications and treatment for people on their assigned caseloads.

Medical progress notes: The section of the individual's record where primary care prescribers document their findings and provide rationale for treatment plans.

RATIONALE:

1. Epilepsy is a chronic health condition experienced by many people with developmental disabilities.
2. The goal of treatment is to minimize the impact of seizures on the lives of people with developmental disabilities. This will be accomplished through:
 - a. early identification, evaluation, and classification of the seizures and type of epilepsy;
 - b. determining the etiology;
 - c. developing a plan of care;
 - d. initiating appropriate treatment;
 - e. adjusting treatment regimes as necessary to achieve optimal seizure control and cognitive performance; and
 - f. providing follow-up care to monitor potential adverse effects of uncontrolled seizures or medications.

EXPECTED OUTCOMES:

Assessment

Medical assessment will be completed and documented in the individual's record.

1. Medical history and physical may include, but not be limited to the following: CBC, serum electrolytes, glucose, calcium, BUN, creatinine, liver profile, urinalysis, EEG, and imaging of the head (e.g., CAT Scan, MRI). Additional information including the date of seizure onset, type and frequency of seizures, description of typical seizures, previous antiepileptic drugs (AEDs) used, and the date of the last seizure should be included in the documentation.
2. Seizure status and tolerance to medication should be documented in the medical progress notes. This should be completed at the time of the annual history and physical for those people whose seizure control is satisfactory and more frequently for those who have active seizure disorders.

EXPECTED OUTCOMES cont'd

3. The seizure frequency, neurological status, and need for neurological consultation should be assessed on a regular basis. The assessment may take place at the time of the annual physical examination and more frequently as needed. Documentation of such assessment should be documented in the progress notes section of the individual's medical record.
4. Every patient who has had a seizure does not need to be followed by a neurologist, but referral should be considered under certain circumstances:
 - a. for people with new onset of seizures
 - b. to confirm the diagnosis of epilepsy
 - c. to clarify seizure type
 - d. to differentiate seizures from non-epileptic movement disorders or behavior
 - e. to obtain recommendations for further evaluation
 - f. to evaluate unexplained abnormalities on the neurological examination
 - g. when there is uncertainty about the etiology of seizures
 - h. when there is failure to achieve optimum control of seizures within 3 months
 - i. when breakthrough occurs after there has been good seizure control with adequate AED levels
 - j. when there is a change in the type of seizure
 - k. when unacceptable side effects indicate the need for alternate therapy choices
 - l. when initial monotherapy trial produces an allergic reaction
 - m. before embarking on combination therapy (polypharmacy)
 - n. when a MRI or CT Brain Scan shows any abnormality
 - o. when further advice is needed regarding driving, employment restrictions, or other safety restrictions
 - p. when considering withdrawal of anticonvulsants
 - q. when the onset or reoccurrence of seizures is associated with declining school performance, behavior disturbances, or developmental regression
 - r. for people who have been seizure-free for 3 to 4 years and still receive anticonvulsant medication,
 - s. when the physician and various team members agree that seizure activity is infrequent and of a brief, mild nature that the individual could be at greater risk from side effects of the medication than effects of seizure activity.

Diagnosis

The epilepsy syndrome should be classified on the basis of history, examination, EEG, and radiographic studies at the discretion of the treating physician. In determining the classification, it should be considered that there is some evidence that certain seizure medications may aggravate specific seizure types (e.g., carbamazepine, phenytoin may worsen myoclonic and/or absence seizures).

Planning

A medical plan of care should be developed and documented in the medical progress notes.

1. Rationale for actual and potential changes in the treatment regime and for diagnostic studies should be documented in the medical progress notes.
2. Orders for medication, laboratory, and other diagnostic tests should be written, signed, and dated on the medical orders sheet.

Implementation

Medical treatment plans should be implemented and documented.

1. Treatment should be initiated using one anticonvulsant, based on current recommendations for seizure type/classification.
2. There should be documentation in the individual's record if the physician and various team members agree that seizure activity is infrequent and of a brief, mild nature that the person could be at greater risk from side effects of the medication than effects of seizure activity.
3. Serum anticonvulsant levels should be completed according to current accepted guidelines on the use of anticonvulsant medications. (See Supporting Information on pages 4-10.)
4. Peak serum anticonvulsant levels will be obtained at any point that drug toxicity is suspected. Trough levels should be obtained if seizures persist or frequency increases.
5. Medications should be adjusted based on the person's clinical and laboratory status. Doses of medication are generally not modified until there has been adequate time to establish responsiveness and for the medication to reach a steady state. Undesirable side effects may indicate the need for dosage reduction or a change in medication. Alterations are contingent on the primary care prescriber's assessment of the person's clinical status and serum anticonvulsant levels. Rationale for changes in medication should be documented in the physicians' progress notes.
6. Abrupt discontinuation of medication should be avoided. When necessary, rationale should be documented in the physicians' progress notes.
7. Seizure control, not serum anticonvulsant levels, should be used as the primary indicator for adjusting doses of medication. When effective seizure control is obtained with doses of anticonvulsants that produce serum anticonvulsant levels above or below the therapeutic range, the primary care prescriber should document the effectiveness and the decision to maintain the dosage as prescribed. (See "Supporting Information" regarding therapeutic levels.)
8. Gradual reduction with eventual discontinuation of anticonvulsant medications may be considered if the person has been seizure free for 3-4 years. Rationale for decisions made should be documented in the medical progress notes.

Evaluation

Evaluation of the seizure management plan should be documented on a regular basis.

1. A summary of the treatment regime should be included in the person's Single Plan.
2. A summary of the types, descriptions, frequency, and duration of the seizure activity should be documented as part of the annual medical history.

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Supporting Information

Laboratory Tests for Long Term Anticonvulsant Therapy

This laboratory schedule is presented as a minimum guideline for patient monitoring. It assumes that the individual is under the daily care of a nurse, shows no overt side effects and that the previous tests were within normal limits. Tests that are repeated annually may be spaced to coincide with the annual physical.

The following laboratory tests refer to hematology, blood chemistry, and urine.

Recommendations for anticonvulsant blood levels are addressed separately on page 6.

NOTE: "CBC" should include a platelet count.

PHENOBARBITAL

1. Baseline CBC, ALT (formerly SGPT), AST, creatinine
2. Repeat CBC, ALT, and AST annually thereafter

PHENYTOIN (DILANTIN)

1. Baseline CBC, ALT (SGPT), AST, creatinine
2. Repeat CBC, ALT and AST in 6 months
3. Repeat CBC, ALT and AST annually thereafter

PRIMIDONE (MYSOLINE)

1. Baseline CBC, ALT (SGPT), AST, creatinine
2. Repeat CBC, ALT, and AST in 6 months
3. Repeat CBC, ALT, and AST annually thereafter

VALPROIC ACID (DEPAKENE, DEPAKOTE)

1. Baseline CBC, ALT (SGPT), AST, creatinine, and urinalysis
2. Repeat CBC, ALT, and AST in 3 months
3. Repeat CBC, ALT, and AST, annually thereafter

CARBAMAZEPINE (TEGRETOL)

1. Baseline CBC, retic count, ALT (SGPT), AST, and creatinine
2. Repeat CBC, ALT, and AST every 3 months for 6 months, then annually.

NOTE: Avoid concomitant treatment with Carbamazepine and "erythromycin-type" antibiotics because the erythromycin may cause Carbamazepine levels to rise to the toxic range.

CLONAZEPAM (KLONOPIN)

1. Baseline CBC, ALT (SGPT), AST and creatinine
2. Repeat CBC, ALT, and AST if clinically indicated

Laboratory Tests for Long Term Anticonvulsant Therapy cont'd**ETHOSUXIMIDE (ZARONTIN)**

1. Baseline CBC, ALT (SGPT), AST, and creatinine
2. Repeat CBC at 3 months
3. Repeat CBC, ALT, and AST annually thereafter

FELBAMATE (FELBATOL)

1. Baseline CBC, differential, retic count, AST, ALT, GGT, Bili, creatinine, urinalysis
2. Retest Liver Functions and CBC every month for 3 months then every 3 months thereafter

GABAPENTIN (NEURONTIN)

1. Baseline CBC, ALT, AST, and creatinine
2. Repeat CBC and creatinine, if clinically indicated

LAMOTRIGINE (LAMICTAL)

1. Baseline CBC, ALT, AST, creatinine
2. Repeat AST, ALT, and/or creatinine, if clinically indicated

CLORAZEPATE (TRANXENE)

1. Baseline CBC, ALT, AST, and creatinine
2. Repeat CBC, ALT, AST annually thereafter

TOPIRAMATE (TOPAMAX)

1. Baseline CBC, CMP, and urinalysis
2. Repeat CBC, BMP, and urinalysis in 3 months and annually thereafter

TIAGABINE (GABITRIL)

1. Baseline CBC, ALT, AST, and creatinine
2. Repeat CBC, ALT, and AST annually thereafter

OXCARBAZEPINE (TRILEPTAL)

1. Baseline CBC, BMP, creatinine, retic count
2. Repeat BMP and CBC annually

ZONISAMIDE (ZONEGRAN)

1. Baseline CBC, ALT, AST, creatinine, urinalysis
2. Repeat CBC, ALT, AST and urinalysis in 6 months, and annually thereafter

LEVETIRACETAM (KEPPRA)

1. Baseline CBC, ALT, AST, creatinine
2. Repeat CBC, ALT and AST annually thereafter

SPECIAL PRECAUTIONS

Elevations of Liver Transaminases

Many of these medications may cause transient elevations of liver transaminases. A slight elevation is usually not clinically significant. If values continue to rise, more frequent monitoring is advised. Dose reduction/discontinuation may be necessary if the lab result is two to three times higher than normal values. Hepatotoxicity occurs most frequently during the first 6 months of new antiepileptic drug (AED) therapy. Although ALT is more specific for liver damage, elevations of AST (SGOT), alkaline phosphatase, LDH, serum bilirubin and prothrombin are all early signs of toxicity.

Osteoporosis

Some antiepileptic drugs (AEDs) may predispose an individual to osteoporosis; therefore, proper monitoring should be performed to ensure that the risk is minimized. The following table lists the medications concerned and the mechanism through which this adverse effect may result.

AEDs Associated with Osteoporosis

BARBITUATES:	Mephobarbital (MEBARAL) Phenobarbital Primidone (MYSOLINE)	Hypocalcemia*
HYDANTOINS:	Phenytoin (DILANTIN)	Osteomalacia (interference with Vitamin D metabolism)
OTHERS:	Topiramate (TOPAMAX)	Osteoporosis $\leq 1\%$

* Barbiturates may increase Vitamin D requirements, possibly by increasing the metabolism of Vitamin D via enzyme induction. Rickets and osteomalacia have rarely been reported following prolonged use of barbiturates.

INDICATORS FOR MEASURING TROUGH SERUM ANTIEPILEPTIC DRUG (AED) LEVELS

1. After an AED has been started, usually 2-3 weeks after initiation of therapy or deletion of an AED during polypharmacy therapy. (See reference table on page 7.)
2. When the individual has to take other medication that may affect the metabolism of the AED(s).
3. Any time an unexpected response occurs.
4. At the first sign of clinical or laboratory toxicity.
5. When medical problems develop, particularly problems involving hepatic, renal, or hematopoietic function.
6. Any unexplained change in clinical status, e.g. "breakthrough" seizure, change in mental status.
7. If compliance with medication regime is a possible issue.
8. If clinical toxicity occurs an AED level may not be necessary depending on the plan of care determined by the treating/consultation physician. For instance, if a plan of care to reduce the dose is made, a medication level is not necessary unless symptoms persist.

ANTIEPILEPTIC DRUG REFERENCE TABLE

Adapted from Clinical Epilepsy and LabCorp Manual

Drug	Level mcg/ml	Time to Steady State	Recommended Timing
Phenobarbital	10 - 40	3 weeks	Trough*
Phenytoin (Dilantin)	5 - 20	1 week	Trough Peak useful if toxicity suspected; Peaks in 3-9 hours
Ethosuximide (Zarontin)	40-100	2 weeks	Trough*
Clonazepam (Klonopin)	15 - 80 mg/ml	2 weeks	Trough, if needed
Primidone (Mysoline) Simultaneously measure Phenobarbital (Pb)	5 - 12	3 weeks due to Pb metabolite	Trough
Valproic Acid (Depakene)	50 - 150	1 week	Trough** Peaks in 1-3 hours
Divalproex Sodium (Depakote)	50 - 150	1 week	Trough** Peaks in 1-3 hours
Carbamazepine (Tegretol)	4 - 12	2 weeks ***	Trough Peaks in 3 hours
Felbamate (Felbatol)	30 - 100	5 days	Trough, if needed
Gabapentin (Neurontin)	4 - 20	2 days	Trough, if needed
Lamotrigine (Lamictal)	2 - 20	5-10 days	Trough, if needed
Topiramate (Topamax)	20 - 50	4 days	Trough, if needed
Tiagabine (Gabitril)	100 - 300 ng/ml	2 days	Trough, if needed
Oxcarbazepine (Trileptal)	10 - 35	3 days	Trough
Levetiracetam (Keppra)	5 - 60	1 day	Trough, if needed
Zonisamide (Zonegran)	10 - 40	5-15 days	Trough, if needed

- * Drugs which have a long-half do not have as much variation between peak and trough levels and either may be used, but should be used consistently. For sake of simplicity, a trough level is suggested.
- ** Drugs such as Depakene, which have a very variable level and a wide therapeutic range, may need several levels to get a better idea of the average level.
- *** Drugs that increase their own rate of metabolism may have a drop in drug blood level after a few weeks. Another level should be done in approximately one month after the initial level. This effect is probably not significant for a dose change during long term therapy because the liver enzymes have already been affected.

REFERENCE DATA

The information listed in the table on the preceding page may be useful in making informed decisions on when to order tests and how to use them. For the sake of simplicity, time to steady state is rounded to the nearest day or week. Levels may be helpful for dosing, evaluating a change in neurologic status, or determining if patients are taking their medication. Newer antiepileptic drugs are included in the table starting with Felbatol. These drugs do not have longstanding established therapeutic ranges and blood levels require clinical correlation.

THERAPEUTIC LEVELS

Most of the antiepileptic drugs (AEDs) have a blood level range which is considered "therapeutic" based on averages. It must be remembered that there will be individuals who will respond to levels either above or below the standard range. The tests measure the total drug concentration, which includes drug which is bound to albumin as well as unbound drug. Since the activity of the drug is based on unbound drug, individuals who have reduced blood proteins, or have their bound anticonvulsant displaced by another drug, may vary in response. They may show toxicity at a level which is generally considered in the therapeutic range or may show therapeutic effect at a level below the range. Other individuals may require higher levels for control and be able to tolerate that level without toxicity. All of this must be considered before simply adjusting a drug dose based on a blood level.

ANTIEPILEPTIC DRUGS (AEDs) IN CHILDREN

Children, much more than adults, have widely varying abilities to absorb, distribute, metabolize and eliminate drugs. AED pharmacokinetics differ qualitatively and quantitatively between children and adults. Although there is physiologic variability associated with age, gender, maturation and health of the patient, drug-specific pharmacokinetics such as saturable metabolism, protein binding and enzyme induction are similar for children and adults.

Formulation and age-dependent variations in absorption play a large role in pediatric plasma AED levels. The rate of absorption generally proceeds in the following order: solutions greater than suspensions; suspensions greater than capsules; capsules greater than tablets; tablets greater than extended-release formulations. The peak rate of metabolism and elimination of most AEDs studied occurs between the ages of 6 months and 2 years. This declines in an exponential manner until reaching adult values in early adolescence. For most AEDs, the half-life is shortened by roughly 50% in the pediatric age range.

As a result of the differences between children and adults, children commonly require more frequent and larger doses relative to body size to attain targeted plasma concentrations.

CONCLUSION

For best results, as well as being able to compare changing levels with clinical findings, it is recommended that all blood to be tested for AED levels be drawn in the morning before any medication is given. The exception would be cases where toxicity is suspected and sampling is requested for the time when the peak level is expected to occur.

When interpreting the test results, individual variation and clinical observation should be kept in mind. As long as toxicity is not a factor, taking one drug to higher levels before adding

another is the preferred approach. This prevents the interactions that can occur with multiple AEDs and simplifies therapy. In trying to simplify existing regimens, withdrawing one drug at a time rather than several simultaneously is recommended. If seizures occur, it is easier to reassess the situation and possibly raise one of the other drugs as the withdrawal process continues.

REFERENCES

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International Classification of Epileptic Seizures

I. Partial seizures (focal seizures with local origin)

A. Simple partial seizures (consciousness not impaired)

1. With motor signs (includes Jacksonian Seizures)
2. With somatosensory or special-sensory symptoms (gustatory, olfactory, auditory, visual, vertiginous)
3. With autonomic signs or symptoms (tachycardia, increased respiration, flushing, pallor, sweating, piloerection, & pupillary dilation)
4. With psychic symptoms (includes dysphagic, dysmnestic (deja vu), cognitive, and affective (fear, anger), illusions, structured hallucinations (music, structured scene)

B. Complex partial seizures (consciousness impaired)

1. Simple partial onset followed by impairment of consciousness.
2. With impaired consciousness at the onset.

C. Partial seizures evolving to secondarily generalized seizures

1. Simple partial leading to generalized seizures.
2. Complex partial leading to generalized seizures.
3. Simple partial leading to complex partial leading to generalized seizures.

II. Generalized seizures (convulsive or nonconvulsive) – *All have loss of consciousness*

A. Absence seizures (typical = petit mal and atypical)

1. Onset in childhood; approximately 40% ending in adolescence (most typical absence) and 50% are replaced by tonic-clonic seizures (most atypical absence).
2. Symptoms include altered awareness or attention and blank stare; may include eye blinking, lip smacking, sticking out the tongue, or rubbing the face; duration 5-30 seconds.
3. Can be mistaken for learning disabilities; behavior; or coordination problems.

B. Myoclonic seizures

1. Characterized by sudden, uncontrollable muscle jerks of one or more extremities or the entire body without obvious impairment of consciousness.
2. Symptoms include symmetrical or asymmetrical, synchronous or asynchronous, single or multiple jerks; possible brief loss of consciousness.
3. Individual is often violently flung to the ground, so that injury is a real possibility. (Helmets are recommended.)

C. Clonic seizures

1. Muscular contractions of the arms, legs, and/or torso with repetition rate slower than myoclonus.
2. Distinct phases may not be observable.
3. Common in childhood.

D. Tonic seizures

1. Symptoms include an abrupt increase in muscle tone (contraction), loss of consciousness, and autonomic signs, lasting from 30 seconds to several minutes.
2. Tonic spasms of truncal and facial muscles associated with flexion of upper limbs and extension of lower limbs.
3. Common in childhood and may result in falls. (Helmets are recommended.)

E. Tonic-clonic seizure (grand mal)**Tonic Phase**

1. May begin suddenly with a shrill cry caused by secondary expulsion of air due to tonic contraction of the trunk muscles.
2. Characterized by rigidity, opisthotonos, and extension of the arms and legs.
3. Jaws may snap shut.
4. Respiration may decrease or cease.
5. Pupils are dilated and unreactive.
6. Heart rate is decreased.
7. Episode is brief -- up to 1 minute. The tonic phase begins to be interrupted by short periods of relaxation followed by another tonic contraction.

Clonic Phase

1. Begins suddenly and ends gradually following tonic phase.
2. Characterized by quick, bilateral severe jerking movements.
3. Stertorous breathing.
4. Autonomic symptoms.
5. Usually lasts less than 1 minute.

Postictal Phase

1. Muscles become flaccid, incontinence may occur as the sphincter muscles relax also.
2. Consciousness gradually returns over 10 to 15 minutes.
3. Amnesia related to the seizure.
4. May need to sleep for a few minutes to 1 hour. Confusion and fatigue may persist for hours or days.

F. Atonic seizures

1. Characterized by abrupt loss of tone in postural muscles, may last only for a few seconds and may occur without loss of consciousness.
2. May be followed by postictal confusion.
3. Injury likely from falls. (Helmets are recommended.)

III. Unclassified epileptic seizures - Such seizures cannot be classified because of inadequate or incomplete data or because they defy classification into the above categories.